DATA EVALUATION RECORD

ETHABOXAM (LGC-30473)
OPPTS (§870.7485, (§85-1))

STUDY TYPE: METABOLISM
MRID 46378533

Prepared for

Health Effects Division
Office of Pesticide Programs
U.S. Environmental Protection Agency
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Arlington, VA 22202

Prepared by

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DATA EVALUATION RECORD

STUDY TYPE: Metabolism -Rat [OPPTS 870.7485 (§85-1); OECD 417].

PC CODE: 090205 **DP BARCODE:** D313732

TEST MATERIAL (PURITY): Ethaboxam (LGC-30473, 98.3% a.i.)
[^{14}C-thiazole]LGC-30473 (≥95% a.i.)
[^{14}C-thiophene]LGC-30473 (≥95% a.i.)

SYNONYMS: *(RS)-N*-(α-cyano-2-thenyl)-4-ethyl-2-(ethylamino)-1,3-thiazole-5-carboxamide

CITATION: Langford-Pollard, A.D. 2003. Metabolism in rats: LGC-30473. Huntingdon Life Sciences, Ltd., Woolley Rd., Alconbury, Huntingdon, Cambridgeshire, PE28 4HS, England. Project Identity No. LKF/019. June 30, 2003. MRID 46378533. Unpublished

SPONSOR: LG Life Sciences, Ltd., Agrochemical Research Center, 104-1, Moonji-dong, Yusong-gu, Daejon, 305-380, Korea.

EXECUTIVE SUMMARY:

In a five-day metabolism study (MRID 46378533), either [^{14}C-thiazole]LGC-30473 or [^{14}C-thiophene]LGC-30473 was administered by oral gavage or cannula (for bile-duct cannulated rats) to groups of Sprague-Dawley rats at doses of 10 or 150 mg/kg. To assess excretion, tissue distribution, and metabolism, groups of 4 rats were administered a single oral dose of 10 or 150 mg/kg of the thiazole or thiophene radiolabeled compound, or 10 mg/kg of the thiazole radiolabeled compound orally once daily for 14 days. Biliary excretion was assessed in groups of 4 bile-duct cannulated rats/sex administered a single dose of 10 or 150 mg/kg of the thiazole labeled compound. Plasma and blood cell pharmacokinetics were assessed in groups of 12 rats/sex administered a single oral dose 10 or 150 mg/kg of the thiazole or thiophene radiolabeled compound, or 10 mg/kg of the thiazole radiolabeled compound orally once daily for 14 days

Mass balance was acceptable for the studies, ranging from 88-94% for the biliary excretion study and 96-105% for the excretion, tissue distribution, and metabolism studies. Most of the radiolabeled compound was excreted in the feces or urine within 48 hours of administration, regardless of radiolabel, dose, or sex. For both radiolabels, fecal and urinary excretion combined accounted for 96-104% of the administered dose. The main route of excretion was feces, accounting for 66-74% of the single or repeated administered low-dose, followed by urine accounting for 23-30% of the administered low-dose. Increasing the dose to 150 mg/kg resulted

30

in more compound being excreted in the feces and less in the urine: fecal excretion accounted for 83-92% of the administered dose, while urine accounted for 13-17% of the administered dose. Results were similar in the biliary excretion study, where the percentage of thiazole radiolabeled compound absorbed in males and females within 48 hours of dosing was 71 and 72%, respectively, for the low dose, and 48 and 61%, respectively, for the high-dose.

Tissue distributions studies demonstrated that minimal amounts (<1% of the dose) of the radiolabeled compound were retained in the tissues up to 120 hours post dosing. The thyroid generally contained the highest μg equivalents/g of the thiazole label, but only minimal amounts of the thiophene label. The liver, kidney, blood cells, and whole blood contained the next highest equivalents, with comparable equivalents measured for both radiolabels.

Pharmacokinetic studies found minimal differences between the thiazole or thiophene label. Except for the longer $t_{1/2}$ in blood cells, blood cell pharmacokinetic values were generally comparable to or lower than plasma values. The $t_{1/2}$ was similar following single administration of both the low- and high-dose, while the C_{max}, t_{cmax}, and the AUC_{120} were higher following the high-dose compared to the low-dose. However, as stated by the author, the increases were not proportional to dose and suggest capacity limited absorption of radioactivity. Compared to single dosing of the thiazole radiolabelled compound, repeated administration of the low-dose resulted in slight increases in plasma C_{max} and notable increases in $t_{1/2}$ and AUC_{120}. Females rats had higher maximum mean plasma radioactivity concentrations, higher plasma AUC_{120}, and longer terminal plasma half-life .

Minimal quantitative differences were noted within the metabolic profiles of urine, feces, or bile from rats administered the same doses of compound with the thiazole or thiophene label, following single or repeated oral administration of the low-dose of the thiazole label, or between sexes. The major urinary radioactive component was LGC-32801, followed by LGC-32800. The major fecal component was the parent compound (LGC-30473), followed by LGC-32802, LGC-32803 and LGC-32801. The main biliary radioactive components were LGC-32801 and LGC-32794.

The metabolism study is classified **Acceptable/Guideline** and satisfies the guideline requirement [OPPTS 870.7485, OECD 417] for a metabolism study in the rat.

COMPLIANCE: Signed and dated GLP, Quality Assurance, and Data Confidentiality statements were provided.

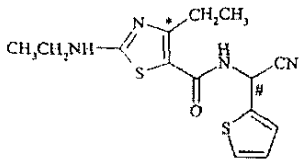
I. MATERIALS AND METHODS:

31

A. MATERIALS:

1. Test compound: LGC-30473

Radiolabeled test material:	[^{14}C-thiazole]LGC-30473
Radiochemical purity	≥ 95%
Specific Activity	26.75 mCi/mmole 1037 MBq/mmol
Lot/Batch #:	SK-09-LG SK-03-HR
Radiolabeled test material:	[^{14}C-thiophene]LGC-30473
Radiochemical purity	≥ 95% determined by HPLC
Specific Activity	27.86 mCi/mmole
Lot/Batch #:	SK-08-LG
Non-radiolabeled test material:	LGC-30473
Description:	white powder
Lot/Batch #:	P980622
Purity:	98.3%
Contaminants:	
CAS # of TGAI:	162650-77-3
Structure:	



* Denotes position of [^{14}C-thiazole] radiolabel
\# Denotes position of [^{14}C-thiophene] radiolabel

2. Vehicle and/or positive control: 1% methylcellulose containing 0.1% Tween 80

3. Test animals:

Species:	rats
Strain:	Sprague-Dawley (Crl:CD® BR)
Age/weight at study initiation:	males and females: 181-263 g; age of animals not stated
Source:	Charles River UK Ltd., Margate, Kent, UK
Housing:	excretion-balance experiments: housed in glass metabolism cages; bile-cannulated rats: housed in restraining cages; plasma radioactivity experiments: housed individually in stainless steel cages with suspended mesh floors
Diet:	VRF1C pellets using d'Alimentation Rationelle, Charles River, UK *ad libitum*
Water:	fresh tap water *ad libitum*
Environmental conditions:	**Temperature:** 21 ± 2°C **Humidity:** 55 ± 15% **Air changes:** approximately 15/hr **Photoperiod:** 12 hrs dark/12 hrs light
Acclimation period:	minimum of 5 days

32

4. Preparation of dosing solutions:

To prepare the stock solutions, the solid radiolabelled test substances were dissolved in acetone and stored at -15°C. For the thiazole radiolabel, two batches of radiolabelled test substance were used: batch number SK-09-LG for Groups 1, 3, 5, 7, 9, and 11, and batch number SK-03-HR for Groups 7, 8, 13, and 14. For the thiophene radiolabel, batch number SK-08-LG was used throughout the entire study.

Dose formulations were freshly prepared on the day of administration. A portion of non-radiolabelled test substance was weighed into a scintillation vial, followed by addition of the appropriate volume of radiolabelled stock solution. The mixture was made up to volume with acetone, concentrated to dryness under nitrogen at 37°C, and stored at -15°C until formulation (generally within 2 hours). The test substance was suspended in 1% methylcellulose containing 0.1% Tween 80 after the pilot excretion/balance experiments (Groups 1 and 2) revealed that the substance would not remain in suspension for the entire dosing duration when only 1% methylcellulose was used. Sample formulations were generally prepared using a sonic probe (1-2 minutes, 3-5 times) with cooling between sonication, followed by mixing on a magnetic stirrer.

To confirm homogeneity and concentration of radioactivity in the dose formulations for each dose group, aliquots of the dose formulations were weighed into volumetric flasks throughout the dosing procedure. The flasks were brought to volume with acetone, and the radioactivity was then measured by liquid scintillation counting (LSC).

B. STUDY DESIGN AND METHODS:

1. **Group arrangements:** Animals were assigned randomly using a random permutation program to the test groups noted in Table 1.

TABLE 1: Dosing groups for pharmacokinetic studies for LGC-30473[a]

Test Group	Experiment type	Radiolabel	Nominal dose level (mg/kg)	No./sex	Remarks
1	Pilot excretion/balance	Thiazole	10	1	urine, feces, and expired air collected up to 120 hr post dosing (study termination); carcass and cagewash retained
2	Pilot excretion/balance	Thiophene	10	1	
3	Main excretion/tissue distribution	Thiazole	10	4	expired air collect up to 48 hr; urine and feces collected up to 120 hr (study termination) for radioactivity counting and metabolism analysis; tissues/ organs and blood sample collected; carcass and cagewash retained
5			150	4	
4	Main excretion/tissue distribution	Thiophene	10	4	urine and feces collected up to 120 hr (study termination) for radioactivity counting and metabolism analysis; tissues/organs and blood sample collected; carcass and cagewash retained
6			150	4	
7	Biliary excretion	Thiazole	10	4	bile, urine, and feces collected up to 48 hr (study termination) for radioactivity counting, bile also for metabolism analysis; G.I. tract, liver, carcass collected; Due to poor recovery, additional 4 ♂ rats dosed with 10 mg/kg and 4 ♀ rats dosed with 150 mg/kg
8			150	4	
9	Plasma/blood cell kinetics	Thiazole	10	12	Each group subdivided into 3 subgroups for blood sample collection: 1: predose, 1, 4, 24, 96 hr 2: 0.25, 2, 6, 48, 120 hr 3: 0.25, 3, 12, 72 hr
11			150	12	
10	Plasma/blood cell kinetics	Thiophene	10	12	
12			150	12	
13	Repeated-dose Excretion/tissue distribution	Thiazole	10	4	dosed once daily for 14 days; urine and feces collected for radioactivity counting and metabolism analysis; at study termination tissue/organs, carcass, cagewash collected
14	Repeated-dose Plasma/blood cell kinetics	Thiazole	10	12	dosed once daily for 14 days; divided into subgroups as Groups 9-12 and blood collected at the various times following the last dose

[a] Data taken from MRID 46378533.

2. **Dosing and sample collection:** The dose solutions were administered orally using a graduated syringe with a rubber gavage tube (Groups 1-6, 9-14) or via a cannula using a graduated syringe (Groups 7, 8). The amount of formulation administered was determined gravimetrically by weighing the dose syringe when loaded and after dosing. The dose volume was 5 mL/kg bw. The nominal specific activity for the doses was 7.5, 0.5, and 3.5 μCi/mg for the low-dose, high-dose, and repeated low-dose experiments, respectively.

34

Radiolabel content was analyzed using liquid scintillation counting (LSC) using LKB-Wallac Model 1219 Rackbeta Spectral or Wallac Model 1409 or 1410 liquid scintillation counters with automatic quench correction. Samples were generally counted for a total of 10 minutes or 40,000 counts, whichever occurred first. HPLC column eluate fractions were generally counted for 4 minutes or 90,000 counts, whichever came first. Before counting, liquid samples were mixed with Ultima Gold or Monoflow 4 scintillator. Samples generated by combustion were absorbed into Carbosorb E CO2 absorbent and mixed with Permafluor E+ scintillator.

a. Expired air: In the pilot study (Groups 1, 2) and thiazole excretion/tissue distribution experiments (Groups 3, 5), air was passed through each cage and the expired volatile radioactivity was trapped by passing the air through two sequential traps containing 2-ethoxyethanol: ethanolamine (3:1, v/v). In the pilot study, the solvents were changed at 6 and 24 hours and then every 24 hours. In the thiazole excretion/tissue distribution experiments, the solvents were replaced at 24 hours, with trapping discontinued at 48 hours.

The trapping solutions were weighed and duplicate aliquots were taken and weighed. Prior to radioassay, methanol was added to each aliquot.

b. Urine: In the pilot study (Groups 1, 2) and excretion/tissue distribution experiments (Groups 3-6), urine was collected separately from each animal into receivers cooled in solid carbon dioxide at 0-6 and 6-24 hours and at 24-hour intervals up to 120 hours. In the bile duct cannulated rat experiments (Groups 7-8), urine was collected at 0-24 and 24-48 hours after dosing. In the repeated-dose excretion/tissue distribution experiment (Group 13), urine was collected separately from each animal into receivers cooled in solid carbon dioxide during the 24-hour periods after doses 1 and 7.

Urine samples were allowed to thaw at room temperature, and water was added to certain samples due to low sample volume. Total weight of each sample was taken. After mixing by inversion, duplicate aliquots were weighed and taken for radioassay.

c. Feces: In the pilot study (Groups 1, 2) and excretion/tissue distribution experiments (Groups 3-6), feces were collected separately from each animal into receivers cooled in solid carbon dioxide at 24-hour intervals up to 120 hours. In the bile duct cannulated rat experiments (Groups 7-8), feces were collected at 0-24 and 24-48 hours after dosing. In the repeated-dose excretion/tissue distribution experiment (Group 13), feces were collected separately from each animal into receivers cooled in solid carbon dioxide during the 24-hour periods after doses 1 and 7.

Fecal samples were thawed at room temperature and transferred to centrifuge pots and homogenized with acetone. The samples were then placed in a sonic bath for 10 minutes. Following centrifugation, the decanted supernatant was weighed and taken for radioassay. Up to four more extractions with acetone or acetone:water were carried out. Remaining fecal residues were air-dried, weighed, and homogenized using a mortar and pestle. Triplicate subsamples were taken for combustion analysis.

d. Blood/plasma: In the plasma/blood cell radioactivity kinetics experiment (Groups 9-12) and the repeated-dose plasma/blood cell radioactivity kinetics experiment (Group 14), blood samples were taken from a tail vein into separate heparinsed tubes. The animals from each experiment were divided into 3 groups, and blood was collected as follows: Subgroup 1: predose, 1, 4, 24, and 96 hours; Subgroup 2: 0.25, 2, 6, 48, and 120 hours; Subgroup 3: 0.25, 3, 12, and 72 hours. Additional blood samples were taken from Group 14 (the repeated-dose plasma/blood cell radioactivity kinetics experiment) immediately before dosing on Days 7 (Subgroup 3) and 14 (Subgroup 1). Each blood sample was stored unfrozen at approximately 4°C until centrifugation to separate the plasma from the cells. Duplicate aliquots of plasma were taken for radioassay, while blood cells were weighed and taken for combustion analysis.

In the excretion/tissue distribution experiment (Groups 3-6), a small sample of blood was drawn by cardiac puncture immediately prior to sacrifice. The sample was divided into 2 portions, one of which was centrifuged to separate plasma. Duplicate aliquots of the plasma were taken for radioassay. Whole blood and blood cells were weighed and taken for combustion analysis.

e. Bile: Bile was collected from the bile duct cannulated rats (Groups 7, 8) at 0-3, 3-6, 6-9, 9-12, 12-24, and 24-48 hours after dosing and "deep frozen." Due to poor recovery of radioactivity, additional rats were dosed (4 male rats at 10 mg/kg and 4 female rats at 150 mg/kg). A fixed volume of water was added to all bile samples and the total weight recorded. Duplicate aliquots were weighed and taken for radioassay.

f. Tissues: In the pilot excretion/balance experiment (Groups 1, 2), carcasses were retained for analysis. Adrenal glands; bone (femur); bone marrow (femur); brain, fat (abdominal); gastrointestinal tract including contents; heart; kidneys; liver; lungs; muscle (skeletal); ovaries and uterus (females); pancreas; pituitary gland; skin without hair; spleen; epididymis, prostate gland, seminal vesicles, and testes (males); and the residual carcass were collected at study termination at 120 hours (5 days) in the excretion/tissue distribution experiments (Groups 3-6), or following the final dose in the repeated-dose excretion/tissue distribution experiment (Group 13). In the bile duct cannulated rat experiments (Groups 7, 8), the gastrointestinal tract including contents, liver, and carcass were collected at study termination at 48 hours.

Carcasses were weighed and solubilized. The digest was weighed and replicate samples were mixed with scintillator and radioassayed. Organs and tissues were prepared for radioassay, with liver, spleen, gastrointestinal tract with contents, and bone samples also prepared for combustion.

g. Cage wash: Cages were washed with water and these washes were retained for analysis in the pilot excretion/balance experiment (Groups 1, 2), excretion/tissue distribution experiments (Groups 3-6), and repeated-dose excretion/tissue distribution experiment (Group 13). Cagewashes were weighed and duplicate aliquots were taken and weighed prior to radioassay.

3. **Pharmacokinetic studies:** Determination of blood kinetics was evaluated in groups of 12 male and 12 female rats given a single oral dose of 10 or 150 mg/kg [^{14}C-thiazole]LGC-

36

30473 (Groups 9, 11) or [^{14}C-thiophene]LGC-30473 (Groups 10, 12), and in a group of 12 male and 12 female rats administered 10 mg/kg [^{14}C-thiazole]LGC-30473 orally daily for 14 days (Group 14). Kinetic parameters (C_{max}, t_{cmax}, AUC, and $t_{1/2}$) were calculated using the software WinNonlin version 3.0.

4. **Metabolite characterization studies:** Urinary, fecal, and biliary metabolite profiles were determined for rats from the single and repeated dose experiments (Groups 3-6 and 13) and the biliary excretion experiment (Groups 7-8). Urine, feces, and bile were pooled according to gender, time interval, and dose group. Radioactive components were quantified using reverse phase high performance liquid chromatography (HPLC). Components were generally quantified using fraction collection data. Certain components were poorly resolved using fraction collection and were quantified using integration of the radiodetector output. Metabolites were identified by comparison of reverse phase HPLC retention times of authentic reference substances and normal phase thin-layer chromatography (TLC). In general, a solution containing a mixture of reference substances was analyzed on each day of HPLC analysis.

   HPLC with radiodetection was performed using a Spectra Physics model SP8800 or Waters 600. Columns, solvent systems, flow rates/elution characteristics, and detectors for the systems were described in detail in the study report (MRID 46378533). For radioactivity determination, a Ramona 5 fitted with a CaF_2 detector cell or Model 9701 radioactivity monitor with a Model 9702 precision mixer was used.

   Normal phase and reversed-phase TLC were used to generate radiochromatograms that were quantified using a Berhold TLC-Linear Analyser. Two-dimensional chromatograms were obtained using an image analyzer and linear-scaled radiochromatograms were generated using TINA software.

5. **Statistics:** The mean and standard deviation were calculated, but it did not appear that any statistical tests were performed.

II. RESULTS:

A. PHARMACOKINETIC STUDIES:

1. **Preliminary (pilot) studies:** The results of the original pilot studies indicated that a dose-formulation problem existed when the test substance suspended in 1% methylcellulose. The pilot experiment using the thiophene label was repeated (Group 2) using 1% methylcellulose with 0.1% Tween 80. This modified vehicle was found to be acceptable and was used in all subsequent experiments.

   Results of the pilot studies indicated that the majority of the radioactivity was excreted within the first 24 hours of dosing. Recovery was greatest in the feces, accounting for 67-73% of the administered dose of [^{14}C-thiazole]LGC-30473 and 65-71% of [^{14}C-thiophene]LGC-30473, with approximately 27-31% and 26-30%, respectively, recovered in the urine. Carcass residual was generally less than 1%. Total recovery as a percentage of the administered dose

was 100.74-101.10% for the Group 1 experiment, and 95.42-97.73% for the Group 2 experiment (using the modified vehicle).

2. **Absorption**: The amount of [C^{14}-thiazole]LGC-30473 absorbed and excreted within 48 hours of a single oral dose is presented in Table 2. At the low-dose (10 mg/kg), males and females absorbed 71 and 72%, respectively, with 23 and 18% not absorbed, respectively. At the high-dose (150 mg/kg), the percentage of the dose absorbed was decreased in males and females, with males absorbing less than females (48% vs. 61%, respectively).

TABLE 2. Time-course of absorption/excretion of radioactivity up to 48 hours after single oral administration of [C^{14}-thiazole]LGC-30473; expressed as % administered dose ± SD[a].

Matrix	Single Dose (Biliary excretion study)			
	10 mg/kg		150 mg/kg	
	Males	Females	Males	Females
Bile				
0-3 hours	14.66 ± 6.55	8.05 ± 2.83	3.17 ± 0.27	1.71 ± 0.77
3-6 hours	12.66 ± 4.78	5.65 ± 0.89	4.57 ± 0.28	2.84 ± 1.46
6-9 hours	8.40 ± 4.94	4.88 ± 1.56	4.21 ± 0.54	2.96 ± 0.97
9-12 hours	4.83 ± 2.67	3.95 ± 1.98	3.01 ± 1.02	2.81 ± 0.66
12-24 hours	4.04 ± 1.70	12.90 ± 9.69	8.24 ± 5.69	13.13 ± 3.01
24-48 hours	0.41 ± 0.08	1.46 ± 1.44	2.66 ± 1.62	12.04 ± 4.84
Subtotal	45.00± 9.44	36.89± 7.52	25.86 ± 5.52	35.47± 6.26
Urine				
0-24 hours	23.42 ± 8.27	27.08 ± 8.45	15.53 ± 2.06	10.87 ± 1.25
24-48 hours	0.51 ± 0.16	4.79 ± 2.34	5.60 ± 4.21	10.68 ± 2.52
Subtotal	23.93 ± 8.39	31.86 ± 9.24	21.12 ± 5.60	21.55 ± 2.50
Cagewash	0.39 ± 0.11	0.37 ± 0.20	0.41 ± 0.20	1.04 ± 0.55
Liver	0.36 ± 0.04	0.61 ± 0.28	0.22 ± 0.07	0.39 ± 0.13
Carcass	1.72 ± 0.60	2.38 ± 1.79	0.87 ± 0.24	2.69 ± 1.58
Total Absorbed	71.40	72.11	48.48	61.14
Feces				
0-24 hours	21.20 ± 2.28	12.37 ± 8.52	33.70 ± 7.10	12.75 ± 13.86
24-48 hours	1.27 ± 0.30	2.47 ± 1.66	5.89 ± 3.32	14.21 ± 4.93
Subtotal	22.47± 2.18	14.84± 9.69	39.59± 4.88	26.96± 12.66
GI Tract	0.04 ± 0.02	3.43 ± 4.97	0.10 ± 0.08	0.72 ± 1.11
Not Absorbed [b]	22.5	18.27	39.69	27.68
Total recovery	93.90 ± 2.23	90.38 ± 6.81	88.17 ± 4.15	88.82 ± 5.39

[a] Data obtained from Table 18-19, pp. 69-70; MRID 46378533.
[b] Estimated by reviewer: Total recovery - total absorbed

3. **Tissue distribution:** Tissue distribution studies demonstrated that minimal amounts of the radiolabelled compound were retained in the tissues up to 120 hours post dosing (see Tables 3-4). In terms of μg equivalents/g, the thiazole label was generally present at the highest concentration in the thyroid, followed by the liver, kidney, blood cells, and whole-blood. The

distribution pattern was similar following the single administration of the low-, high, or repeated low-dose. Slightly higher concentrations were generally measured in these tissues from the high-dose and repeated low-dose animals compared to those in the single low-dose groups.

Following administration of the thiophene label, the liver, kidney, blood cells, whole blood, and skin (high-dose males) contained the highest μg equivalents/g equivalent of the label. Unlike the thiazole label, thyroid did not accumulate notable amounts of the thiophene label.

TABLE 3: Distribution of radioactivity in selected tissues/organs as μg equivalents/g ± SD (except as noted) up to 120 hours after single or repeated oral administration of [C^{14}-thiazole]LGC-30473[a].

Tissue/organ	Single Dose				Repeated Dose	
	10 mg/kg (Group 3)		150 mg/kg (Group 5)		10 mg/kg (Group 13)	
	Males	Females	Males	Females	Males	Females
Thyroid	4.13 ± 4.20	4.82 ± 3.49	9.71 ± -	not detected	10.9 ±4.03	2.36 ± 1.70
Liver	0.361 ± 0.051	0.537 ± 0.124	2.77 ± 0.973	3.40 ± 0.726	1.81 ± 0.348	2.86 ± 0.289
Kidney	0.181 ± 0.012	0.196 ± 0.019	1.75 ± 0.349	1.78 ± 0.441	1.22 ± 0.354	1.63 ± 0.288
Blood cells	0.162 ± 0.015	0.253 ± 0.077	1.47 ± 0.517	1.58 ± 0.504	1.68 ± 0.389	2.45 ± 0.926
Whole-blood	0.095 ± 0.014	0.126 ± 0.030	1.00 ± 0.271	0.997± 0.280	0.972 ± 0.223	1.20 ± 0.252
Skin	0.088 ± 0.056	0.044 ± 0.004	0.428± 0.165	0.220± 0.044	0.675 ± 0.053	0.317 ± 0.070
Total (% dose in total tissue)[b]	0.71 ± 0.18	0.74 ± 0.15	0.36 ± 0.16	0.27 ± 0.10	not provided	not provided
Carcass (% administered dose)	0.74 ± 0.07	0.54 ± 0.03	0.51 ± 0.19	0.31 ± 0.13	3.16 ± 0.64	2.69 ± 0.23

[a] Data obtained from Tables 4- 6, 8-9, 37-38 on pp. 55-57, 59-60, 88-89; MRID 46378533.
[b] Excludes plasma and blood cells

TABLE 4: Distribution of radioactivity in selected tissues/organs as μg equivalents/g ± SD (except as noted) up to 120 hours after single oral administration of [C^{14}-thiophene]LGC-30473[a].

Tissue/organ	Single Dose			
	10 mg/kg (Group 4)		150 mg/kg (Group 6)	
	Males	Females	Males	Females
Thyroid	0.058 ± 0.067	0.147 ± 0.110	0.418± 0.835	not detected
Liver	0.222 ± 0.025	0.543 ± 0.062	2.67 ± 0.590	3.41 ± 0.618
Kidney	0.213 ± 0.014	0.311 ± 0.010	1.39 ± 0.200	1.64 ± 0.083
Blood cells	0.203 ± 0.044	0.356 ± 0.045	3.90 ± 0.586	2.95 ± 0.320
Whole-blood	0.112 ± 0.017	0.195 ± 0.014	1.51 ± 0.450	1.86 ± 0.864
Skin	0.061 ± 0.028	0.036 ± 0.001	2.17 ± 0.357	0.309 ± 0.065
Total (% dose in total tissue)[b]	0.49 ± 0.03	0.64 ± 0.03	0.63 ± 0.11	0.38 ± 0.07
Carcass (% administered dose)	0.40 ± 0.13	0.49 ± 0.13	0.29 ± 0.06	0.32 ± 0.09

[a] Data obtained from Tables 11-13, 15-16 on pp. 62-64, 66-67, MRID 46378533.
[b] Excludes plasma and blood cells

4. **Excretion**: Most of the radiolabelled compound was excreted in the feces or urine within 24 hours of administration, regardless of radiolabel, dose, or sex (see Tables 5 and 6). By 120 hours post dosing, little of the compound remained. For both radiolabels, fecal and urinary excretion combined accounted for 96-104% of the administered dose. The main route of excretion was feces, which accounted for 66-77% of the administered 10 mg/kg dose recovered over 120 hours following both single and repeated dosing. Urine was also a notable route of excretion, accounting for 23-30% of the administered 10 mg/kg dose. Single administration of 150 mg/kg resulted in slightly more compound being excreted in the feces and less in the urine: fecal excretion accounted for 83-92% of the administered dose, while urine accounted for 13-17% of the administered dose.

40

TABLE 5. Recovery/excretion of radioactivity up to 120 hours following single or repeated oral administration of [^{14}C-thiazole]LGC-30473; expressed as % administered dose ± SD[a].

Tissue/organ	Single Dose				Repeated Dose [b]	
	10 mg/kg (Group 3)		150 mg/kg (Group 5)		10 mg/kg (Group 13)	
	Males	Females	Males	Females	Males	Females
Urine						
0-6 hr	14.07 ± 4.90	13.97 ± 6.03	2.50 ± 1.15	3.22 ± 1.26	12.64 ± 1.73	14.31 ± 1.93
6-24 hr	13.24 ± 4.96	14.32 ± 6.54	12.73 ± 3.81	8.29 ± 2.65	8.84 ± 2.23	8.61 ± 1.77
24-48 hr	0.67 ± 0.19	0.77 ± 0.20	1.75 ± 1.02	0.97 ± 0.36	0.77 ± 0.13	1.36 ± 0.33
Total [c]	28.29 ± 1.42	29.86 ± 1.12	17.28 ± 4.91	12.71 ± 3.87	23.02 ± 1.62	26.02 ± 1.68
Feces						
0-24 hr	62.16 ± 4.38	60.47 ± 1.80	74.67 ± 14.17	85.87 ± 7.63	70.05 ± 2.31	66.55 ± 6.25
24-48 hr	5.07 ± 3.84	4.87 ± 1.56	8.13 ± 5.69	5.34 ± 4.8	3.08 ± 1.67	4.99 ± 2.70
Total [c]	67.83 ± 0.44	66.10 ± 0.89	83.83 ± 8.62	91.62 ± 2.97	74.35 ± 2.20	73.33 ± 3.90
Cagewash	0.05 ± 0.05	0.21 ± 0.17	0.11 ± 0.08	0.19 ± 0.27	0.31 ± 0.32	0.53 ± 0.38
Total expired air	0.67 ± 0.11	0.67 ± 0.14	0.31 ± 0.15	0.31 ± 0.09	Not measured	Not measured
Carcass	0.74 ± 0.07	0.54 ± 0.03	0.51 ± 0.19	0.31 ± 0.13	3.16 ± 0.64	2.69 ± 0.23
Total	97.59 ± 1.39	97.38 ± 1.58	102.02 ± 5.32	105.13 ± 1.56	100.84 ± 2.39	102.56 ± 4.85

[a] Data obtained from Table 4 and 37, pp. 55 and 88; MRID 46378533.

[b] Day 14 values reported

[c] The total includes the values for the 48-72, 72-96, and 96-120 hour collection periods: these values were less than 1% of the administered dose

TABLE 6. Recovery/excretion of radioactivity up to 120 hours following a single oral administration of [^{14}C-thiophene]LGC-30473; expressed as % administered dose ± SD[a].

Tissue/organ	Dose			
	10 mg/kg (Group 4)		150 mg/kg (Group 6)	
	Males	Females	Males	Females
Urine				
0-6 hr	16.28 ± 2.05	14.89 ± 2.59	4.08 ± 2.31	2.45 ± 1.54
6-24 hr	9.38 ± 1.20	12.24 ± 1.55	10.88 ± 3.23	11.33 ± 2.24
24-48 hr	0.93 ± 0.19	2.08 ± 0.68	0.56 ± 0.17	0.80 ± 0.34
Total [b]	27.05 ± 3.38	29.84 ± 3.12	15.91 ± 1.89	14.97 ± 1.31
Feces				
0-24 hr	72.28 ± 5.66	46.79 ± 12.04	78.38 ± 4.22	79.67 ± 2.50
24-48 hr	4.17 ± 1.25	20.26 ± 9.32	3.26 ± 1.40	3.42 ± 1.73
Total [b]	77.11 ± 5.83	69.10 ± 3.13	82.28 ± 2.87	83.76 ± 1.25
Cagewash	0.11 ± 0.04	0.11 ± 0.11	0.10 ± 0.07	0.12 ± 0.08
Carcass	0.40 ± 0.13	0.49 ± 0.13	0.29 ± 0.06	0.32 ± 0.09
Total	104.66 ± 3.81	99.53 ± 2.06	95.58 ± 0.87	99.17 ± 0.42

[a] Data obtained from Table 11, p. 62; MRID 46378533.

[b] The total includes the values for the 48-72, 72-96, and 96-120 hour collection periods: these values were less than 1% of the administered dose

5. Pharmacokinetics:

The pharmacokinetic values of [C^{14}-thiazole]LGC-30473 in the plasma or blood of rats following a single oral dose of 10 or 150 mg/kg or repeated administration of 10 mg/kg are presented in Table 7, while the pharmacokinetic values of [C^{14}-thiophene]LGC-30473 in the plasma or blood of rats following a single oral dose of 10 or 150 mg/kg are presented in Table 8. In general, there appear to be minimal differences between the thiazole or thiophene label in the pharmacokinetics in plasma or blood. Females tended to have increased C_{max} and AUC_{120} values compared to males, but it is not known if the increases were statistically significant. Compared to the low-dose, single administration of the high-dose resulted in increased values of C_{max} (~6-11-fold), t_{cmax} (~2-4-fold), and AUC_{120} (~9-11-fold) in males and females, while $t_{1/2}$ was not consistently affected. Repeated dosing resulted in higher values of C_{max} (1.2-1.3-fold), $t_{1/2}$ (1.2-1.9-fold), and AUC_{120} (~2-6-fold).

47

TABLE 7. Kinetic parameters in the plasma and blood of rats following single or repeated oral administration of [^{14}C-thiazole]LGC-30473[a].

Parameter	Single Dose				Repeated Dose [b]	
	10 mg/kg (Group 9)		150 mg/kg (Group 11)		10 mg/kg (Group 14)	
	Males	Females	Males	Females	Males	Females
PLASMA						
C_{max} (mean; µg-eq/g)	2.31	3.09	14.5	19.7	3.08	3.81
t_{cmax} (hrs)	1	2	3	6	3	1
$t_{1/2}$ (hrs)	30.5	37.7	31.5	36.0 [c]	46.9	56.4 [c]
AUC_{120} (µg-eq/g ·hr)	32.7	38.1	367.7	448.8	70.8	83.0
BLOOD						
C_{max} (mean; µg-eq/g)	1.16	1.90	9.13	14.9	3.37	5.14
t_{cmax} (hrs)	1	2	4	6	3	2
$t_{1/2}$ (hrs)	114.3 [c]	109.6 [c]	69.3 [c]	107.2 [c]	142.5 [c]	213.4 [c]
AUC_{120} (µg-eq/g ·hr)	36.3	51.2	356.7	497.4	167.4	294.7

[a] Data obtained from Tables 22, 25, 34, and 35 on pp. 73, 76, 85, and 86; MRID 46378533.
[b] Day 14 values reported
[c] The parameter is an estimate since the data did not meet the acceptance criteria specified in "Pharmacokinetic analysis" (p. 36, MRID 46378533).

TABLE 8. Kinetic parameters in the blood of rats following single oral administration of [^{14}C-thiophene]LGC-30473[a].

Parameter	10 mg/kg (Group 10)		150 mg/kg (Group 12)	
	Males	Females	Males	Females
PLASMA				
C_{max} (mean; µg-eq/g)	2.23	2.80	17.8	21.0
t_{cmax} (hrs)	2	1	4	4
$t_{1/2}$ (hrs)	33.7	40.6	31.8	36.4
AUC_{120} (µg-eq/g ·hr)	31.2	36.9	350.0	411.1
BLOOD				
C_{max} (mean; µg-eq/g)	1.08	1.81	12.4	17.0
t_{cmax} (hrs)	2	2	4	4
$t_{1/2}$ (hrs)	124.1 [b]	162.2 [b]	96.6 [b]	129.4 [b]
AUC_{120} (µg-eq/g ·hr)	37.7	53.9	394.4	507.1

[a] Data obtained from Tables 28, 31 on pp. 79, 82; MRID 46378533.
[b] The parameter is an estimate since the data did not meet the acceptance criteria specified in "Pharmacokinetic analysis" (p. 36, MRID 46378533).

C. METABOLITE CHARACTERIZATION STUDIES:

The author assigned the prefix Tz or Tp to the metabolic component to represent the thiazole and thiophene labels, respectively. The U, FE, and B designations denote urine, feces, and bile, respectively.

1. **Urine:** A total of 22 components were isolated in the urine of male and female rats receiving a single or repeated oral dose of [^{14}C-thiazole]- or [^{14}C-thiophene]-LGC-30473. The components accounting for 2% or more of the administered dose are summarized in Tables 9 and 10. Minimal quantitative differences were noted between the metabolic profiles of rats treated with the thiazole or thiophene label, following single or repeated oral administration of the low-dose of the thiazole label, or between sexes. While the overall amount of urinary radioactivity as a percentage of the administered dose was decreased following single oral administration of the high-dose compared to the low dose, minimal qualitative differences were observed between metabolic profiles.

   The major radioactive component was U13 (LGC-32801), accounting for 7.8-9.9% of the single low-dose, 2.7-3.1% of the high-dose, and 6.9-7.2% of the repeated low-dose. A minor metabolite, U13a, was partially separated from the major metabolite U13 using radiodetector output. No other metabolite represented more than 3% of the administered dose.

   Glucuronide and sulphate conjugates were not detected when samples of urine from male rats in Group 3 (single oral dose of 10 mg/kg) were treated with β-glucuronidase/sulphatase. Acid/base treatment of the urine resulted in an increase in the proportion of the polar fraction, while the proportion of the non-polar metabolite TzU17 decreased after base treatment.

TABLE 9. Urinary metabolite profile in rats at 48 hours following single or repeated oral dose of [^{14}C-thiazole]LGC-30473; expressed as % administered dose[a].

Metabolite	Single Dose				Repeated Dose (Day 14; % daily dose)	
	10 mg/kg (Group 3)		150 mg/kg (Group 5)		10 mg/kg (Group 13)	
	Males	Females	Males	Females	Males	Females
TzU13 [b] (LGC-32801)	7.8	9.9	3.1	3.1	7.2	6.9
TzU17 (LGC-32800)	2.2	2.9	2.1	1.5	1.2	2.3
Total identified [c]	10	12.8	5.2	4.6	8.4	9.2
TzU1	2.7	2.0	0.7	0.4	1	1.5
TzU2	2.6	2.0	2.3	1.4	2.3	1.8
TzU11	1.1	0.9	0.8	0.5	1.0	0.9
TzU12	1.1	1.0	0.8	0.6	0.8	0.6
TzU13a [b]	1.7	1.4	0.6	0.6	1.3	2.4
Total unidentified [d]	17.48	15.76	11.38	6.98	12.95	14.68
Others (unaccounted for) [e]	0.5	0.5	0.4	0.9	0.9	0.4
Total urinary radioactivity	27.98	29.06	16.98	12.48	22.25	24.28

[a] Data obtained from Tables 43-44 and 62, pp. 94-95, 112-113 in MRID 46378533.
[b] Components quantified using integration of radiodetector output as they were poorly resolved by fraction collection
[c] Rough estimate calculated by reviewer: total of the means
[d] Only the components comprising 2% or more of the administered dose are summarized above, but the rough estimate (calculated by the reviewer) of the total unidentified includes all unidentified components;
Total unidentified = Total radioactivity - (total identified + others)
[e] Totaled by study author: 100 - sum of components

TABLE 10. Urinary metabolite profile in rats at 48 hours following single oral dose of [^{14}C-thiophene]LGC-30473; expressed as % administered dose[a].

Metabolite	Single Dose			
	10 mg/kg (Group 4)		150 mg/kg (Group 6)	
	Males	Females	Males	Females
TpU13 [b] (LGC-32801)	8.5	9.2	2.7	2.9
TzU17 (LGC-32800)	2.3	2.7	1.6	2.1
Total identified [c]	10.8	11.9	4.3	5.0
TpU5	2.3	2.1	1.7	1.3
TpU9	1.3	1.9	1.7	1.1
TpU10	1.1	1.1	0.7	0.8
TpU11	1.0	1.4	0.7	0.5
TpU12	1.3	1.1	0.9	0.6
TpU13a [b]	1.0	1.1	0.5	0.6
Total unidentified [d]	15.09	16.71	11.12	9.38
Others (unaccounted for) [e]	0.7	0.6	0.1	0.2
Total urinary radioactivity	26.59	29.21	15.52	14.58

[a] Data obtained from Tables 48-49, pp. 99-100, in MRID 46378533.
[b] Components quantified using integration of radiodetector output as they were poorly resolved by fraction collection
[c] Rough estimate calculated by reviewer: total of the means
[d] Only the components comprising 2% or more of the administered dose are summarized above, but the rough estimate (calculated by the reviewer) of the total unidentified includes all unidentified components;
Total unidentified = Total radioactivity - (total identified + others)
[e] Totaled by study author: 100 - sum of components

2. **Feces:** A total of 27 components were isolated in the feces of male and female rats receiving single or repeated oral doses of [^{14}C-thiazole]- or [^{14}C-thiophene]-LGC-30473. The components accounting for 2% or more of the administered dose are summarized in Tables 11 and 12. Minimal quantitative differences were noted between rats administered the thiazole or thiophene label, following single or repeated oral administration of the low-dose of the thiazole label, or between sexes. The most significant difference between the fecal metabolic profiles of rats following single administration of the low- or high-dose was the increased percentage of parent compound recovered in high-dose rats compared to low dose rats.

   The major radioactive component was FE25 (LGC-30473; parent compound), accounting for 5.9-17.3% of the single low-dose, 46.9-68.3% of the high-dose, and 14.5-18.0% of the

repeated low-dose. The next major component was FE17 (LGC-32802), followed by FE15 (LGC-32803) and FE14 (major portion identified as LGC-32801).

TABLE 11. Fecal metabolite profile in rats at 48 hours following single or repeated oral dose of [^{14}C-thiazole]LGC-30473; expressed as % administered dose[a].

Metabolite	Single Dose				Repeated Dose (Day 14; % daily dose)	
	10 mg/kg (Group 3)		150 mg/kg (Group 5)		10 mg/kg (Group 13)	
	Males	Females	Males	Females	Males	Females
Parent -TzFE25 (LGC-30473)	10.1	5.9	50.5	68.3	14.5	18.0
TzFE14 [b] (LGC-32801)	5.3	5.1	1.9	1.2	3.8	4.1
TzFE15 (LGC-32803)	6.2	4.8	3.6	2.3	4.1	4.7
TzFE17 (LGC-32802)	9.1	10.8	5.2	3.4	7.5	9.5
Total identified [c]	30.7	26.6	61.2	75.2	29.9	36.3
TzFE1	3.3	4.0	2.0	2.2	3.3	4.7
TzFE12	3.6	3.3	1.8	0.4	2.0	1.4
TzFE13	3.0	2.8	2.0	0.6	4.4	1.5
TzFE16	2.0	2.9	1.3	0.6	1.6	1.7
TzFE18	1.8	2.4	0.3	<0.3	1.2	0.9
Total unidentified [d]	23.47	24.01	9.63	7.44	17.37	12.66
Others (unaccounted for) [e]	1.8	3.5	6.4	5.3	10.8	7.8
Total fecal radioactivity	55.97	54.11	77.23	87.94	58.07	56.76

[a] Data obtained from Tables 51, 53 and 63-64, pp. 102, 104, and 114-115 in MRID 46378533.

[b] Resolved into several components - each which accounted for less than 5% of the dose; major portion identified as LGC-32801 (see page 18, MRID 46378533)

[c] Rough estimate calculated by reviewer: total of the means

[d] Only the components comprising 2% or more of the administered dose are summarized above, but the rough estimate (calculated by the reviewer) of the total unidentified includes all unidentified components;

Total unidentified = Total radioactivity - (total identified + others)

[e] Totaled by study author: 100 - sum of components

47

TABLE 12. Fecal metabolite profile in rats at 48 hours following single oral dose of [^{14}C-thiophene]LGC-30473; expressed as % administered dose[a].

Metabolite	Single Dose			
	10 mg/kg (Group 4)		150 mg/kg (Group 6)	
	Males	Females	Males	Females
Parent - TpFE25 (LGC-30473)	17.3	14.0	46.9	53.6
TpFE14 [b] **(LGC-32801)**	4.2	4.9	2.3	1.6
TpFE15 (LGC-32803)	5.8	5.1	4.0	3.5
TpFE17 (LGC-32802)	9.5	6.5	4.3	4.2
Total identified [c]	36.8	30.5	57.5	62.9
TpFE1	2.7	2.3	1.8	1.8
TpFE12	2.4	3.2	0.9	0.6
TpFE13	3.0	3.6	1.8	1.3
TpFE16	2.4	2.0	1.5	1.7
TpFE18	2.0	1.9	0.9	0.6
Total unidentified [d]	24.41	24.09	14.13	10.97
Others (unaccounted for) [e]	4.5	2.2	4.3	4.8
Total fecal radioactivity	65.71	56.79	76.03	78.67

[a] Data obtained from Tables 54 and 56, pp. 105 and 107; MRID 46378533.
[b] Resolved into several components - each which accounted for less than 5% of the dose; major portion identified as LGC-32801 (see page 18, MRID 46378533)
[c] Rough estimate calculated by reviewer: total of the means
[d] Only the components comprising 2% or more of the administered dose are summarized above, but the rough estimate (calculated by the reviewer) of the total unidentified includes all unidentified components;
Total unidentified = Total radioactivity - (total identified + others)
[e] Totaled by study author: 100 - sum of components

3. **Bile:** A total of 26 components were isolated in the bile of male and female rats receiving a single oral low- or high-dose of [^{14}C-thiazole]-LGC-30473. The components accounting for 2% or more of the administered dose are summarized in Table 13. Minimal quantitative differences were noted between the biliary metabolic profiles of rats following administration of the low- or high-dose, and only minimal sex differences were present. The main radioactive components were B15 (accounting for 2.2-6.3% and 2.7-3.0% of the low- and high-dose, respectively) and B22 (accounting for 4.7-6.7% and 3.0-4.0% of the low- and high-dose, respectively). Component B15 corresponded to the major metabolite U13 (LGC-32801), while B22 corresponded to the minor fecal metabolite FE19 (LGC-32794). Enzyme deconjugation experiments using β-glucuronidase/sulphatase demonstrated that B15, B22,

48

and U13 (corresponding to B15) were stable to treatment (i.e., there were no glucuronide of sulphate conjugates present).

TABLE 13. Biliary metabolite profile in rats at 48 hours following single oral dose of [^{14}C-thiazole]LGC-30473; expressed as % administered dose[a].

Metabolite	Single Dose			
	10 mg/kg (Group 7)		150 mg/kg (Group 8)	
	Males	Females	Males	Females
TzB15 [b] **(LGC-32801)**	6.3	2.2	2.7	3.0
TzB22 (LGC-32794)	4.7	6.7	3.0	4.0
Total identified [c]	11	8.9	5.7	7.0
TzB2	2.0	2.4	1.1	1.6
TzB3	2.8	1.8	2.0	2.6
TzB13	3.0	1.6	1.8	2.3
TzB15a [b]	1.7	1.0	1.2	1.9
Total unidentified [d]	32.1	26.39	19.26	27.17
Others (unaccounted for) [e]	1.9	1.6	0.9	1.3
Total biliary radioactivity	45.00	36.89	25.86	35.47

[a] Data obtained from Tables 57-58, pp. 108-109; MRID 46378533.
[b] Component quantified using integration of the radiodetector output as they were poorly resolved by fraction collection
[c] Rough estimate calculated by reviewer: total of the means
[d] Only the components comprising 2% or more of the administered dose are summarized above, but the rough estimate (calculated by the reviewer) of the total unidentified includes all unidentified components;
Total unidentified = Total radioactivity - (total identified + others)
[e] Totaled by study author: 100 - sum of components

4. **Liver:** A total of 14 components were isolated in the enzyme-treated liver of male rats receiving a single or repeated oral low-dose of [^{14}C-thiazole]-LGC-30473. The components accounting for 5% or more are presented in Table 14. It was stated that the liver profile was similar to the urinary metabolic profile.

TABLE 14. Liver metabolite profile in rats at 120 hours following single or repeated oral dosing of [^{14}C-thiazole]LGC-30473; expressed as % liver activity[a].

Metabolite	10 mg/kg		
	Single dose (Group 3) [b]	Repeated dose (Group 13)	
	Males	Males	Females
TzL1	11.8	8.9	11.1
TzL6	5.0	2.7	1.6
TzL7	2.1	5.5	1.8
TzL8	1.8	5.5	7.7
TzL9	2.7	5.6	4.6
TzL11 (LGC-32801)	14.4	13.3	11.7
TzL13	3.1	6.6	6.0
Others (unaccounted for) [d]	1.9	2.0	4.4
Total extract	62.8	76.3	77.3

[a] Data obtained from Tables 65-66, pp. 116-117; MRID 46378533.
[b] Metabolites are not separated into "Identified" or "Unidentified" because the author did not clearly state if other components besides Tz11 corresponded to identified metabolites
[c] Female data not reported because of poor recoveries of radioactivity from the HPLC column
[d] Totaled by study author: 100 - sum of components

5. **Metabolic pathway:** The proposed biotransformation pathway is actually presented in a separate reference (Reference 1 in MRID 46378533; not included with the study). The summary provided in MRID 46378533 is as follows: LGC-30473 was N-deethylated to form LGC-32794 followed by oxidation of the thiazole sulfur to LGC-32800. LGC-30473 also underwent enolisation. In one pathway, the enol form underwent hydrolysis to the amide LGC-32801, while in the other pathway, the enol underwent sulfate conjugation to LGC-32802 and hydroxylation/sulfate conjugation to LGC-32803.

III. DISCUSSION and CONCLUSIONS:

A. INVESTIGATORS' CONCLUSIONS:

The study (MRID 46378533) was conducted to evaluate the absorption, distribution, metabolism, and excretion of [^{14}C-thiazole]LGC-30473 and [^{14}C-thiophene]LGC-30473 in rats after single oral doses at 10 and 150 mg/kg and repeat oral doses (thiazole radiolabel only) for 14 consecutive days at 10 mg/kg. Biliary excretion in bile duct cannulated rats was also evaluated after single doses of at 10 and 150 mg/kg of [^{14}C-thiazole]LGC-30473.

Excretion of radioactivity was rapid after single doses or following the final dose of repeated exposures with >90% of the dose excreted within 48 hours after dosing. The largest percentage

50

of radioactivity was excreted in the feces, followed by the urine. Urinary excretion was higher at the low dose level than the high dose level. No substantial differences in patterns of excretion were noted with the regard to the radiolabelled form, sex, or between single and repeat low level oral doses of [^{14}C-thiazole]LGC-30473.

The biliary excretion studies demonstrated that absorption was higher at the low dose level than the high dose level. Absorption was similar in male and female rats at the low dose level (~72%) but was higher in female rats (61%) than male rats (48%) at the high dose level.

The pharmacokinetic data indicated that there were no substantiative differences between the radiolabelled forms in plasma or blood cell mean radioactivity in male or female rats. Compared to male rats, female rats had higher maximum mean plasma radioactivity concentrations (~1.2 - 1.3-fold higher), higher plasma AUC_{120} (~ 1.2 fold higher), and longer terminal plasma half-life. Similar findings were noted in the pharmacokinetic parameters in blood cells. Increasing the dose from 10 to 150 mg/kg increased both the C_{max} and AUC_{120} values for plasma and red cells, but the increases were less than the proportionate dose increase and suggested saturated absorption of radioactivity. Increasing the dose appeared to have little effect of the terminal half-life of plasma or blood cell radioactivity.

Highest mean tissue concentrations of radioactivity following single administration of the low and high dose of [^{14}C-thiazole]LGC-30473 were detected in the thyroid and liver. While administration of the high-dose increased the tissue concentrations, the increase was not proportionate to dose. Mean tissue radioactivity concentrations following 14-day consecutive daily doses of 10 mg/kg were generally 5-10-fold those after a single oral dose of 10 mg/kg and were highest in the thyroid, liver, and blood cells. Highest mean tissue concentrations of radioactivity following single administration of the low and high dose of [^{14}C-thiophene]LGC-30473 were detected in the liver, blood cells, kidneys (low dose), whole blood, and skin (high-dose males). Again, while the administration of the high-dose increased the tissue concentrations, increases were not proportionate to dose. Overall tissue accumulation of radioactivity was low after single oral doses with only a small percentage of the dose retained in the tissues at 120 hours.

Identification of unknown metabolites and a proposed biotransformation pathway are to be reported in a separate study (cited as Reference 1 in MRID 46378533). Following administration of both the low- and high-dose of radiolabels, the primary metabolite recovered in the urine was U13 (LGC-32801), while metabolites in feces included FE14 (major portion identified as LGC-32801), FE15 (LGC-32803), FE17 (LGC-32802), and parent compound (LGC-30473). The amount of parent compound recovered in the feces was greatly increased at the high-dose compared to the low dose. Biliary metabolites included B15 (corresponding to U13, LGC-32801) and TzB22 (LGC-32794).

B: <u>REVIEWER COMMENTS</u>:

Mass balance was acceptable for the studies. No notable differences in the two radiolabels were noted in any parameters. Most of the radiolabelled compound was excreted in the feces or urine within 48 hours of administration, regardless of radiolabel, dose, or sex. The main route of excretion was feces, followed by the urine. Minimal amounts of radioactivity were recovered in

51

expired air or cage wash, and less than 3.2% remained in the carcass even following repeated dosing. Tissue distribution studies demonstrated that minimal amounts of radiolabelled compound were retained in the tissues. The thyroid generally contained the highest μg equivalents/g of the thiazole label, but only minimal amounts of the thiophene label. The liver, kidney, blood cells, whole blood, and skin contained the next highest equivalents, with comparable equivalents measured for both radiolabels (except skin, which retained more radioactivity only in the males administered the high-dose, thiophene labeled compound).

High-dose rats absorbed a smaller percentage of compound compared to the low-dose as demonstrated by the absorption study, by the excretion study reporting increased amounts of compound recovered in the feces at the high-dose, and by the fecal metabolite profile studies, which reported a greatly increased percentage of parent compound in the feces in the high-dose group. Males absorbed less than females at the high dose.

Pharmacokinetic studies found minimal differences between the thiazole or thiophene label. Except for the elimination half-life ($t_{1/2}$) (blood cell $t_{1/2}$ ~ 69-162 hours; plasma $t_{1/2}$ ~ 31-41 hours), blood cell pharmacokinetic values were generally comparable to or lower than plasma values. Differences were noted between the low- and high-dose pharmacokinetics. While the $t_{1/2}$ of LGC-30473 was similar following single administration of both the low- and high-dose (plasma values: 31-41 hours and 32-36 hours, respectively), the maximum concentration (C_{max}), time to maximum concentration (t_{cmax}), and the area under the curve at 120 hours (AUC_{120}) were higher following the high-dose (plasma values: 15-21 μg-eq/g, 3-6 hours, and 350-449 μg-eq/g·hr, respectively) compared to the low-dose (plasma values: 2-3 μg-eq/g, 1-2 hours, and 31-37 μg-eq/g·hr, respectively). Compared to a single dose of the thiazole radiolabeled compound, repeated administration of the low-dose resulted in slight increases in plasma C_{max} and notable increases in $t_{1/2}$ and AUC_{120}. Females rats had higher maximum mean plasma radioactivity concentrations, higher plasma AUC_{120}, and longer terminal plasma half-life .

Minimal quantitative differences were noted within the metabolic profiles of urine, feces, or bile from rats administered the same doses of compound with the thiazole or thiophene label, following single or repeated oral administration of the low-dose of the thiazole label, or between sexes. The major urinary radioactive component was LGC-32801 (6.9-9.9% of single or repeated low-dose; 2.7-3.1% of high-dose), followed by LGC-32800 (recovery < 3% of dose). The major fecal component was the parent compound (LGC-30473; 5.9-18% of single or repeated low-dose; 46.9-68.3% of high-dose), followed by LGC-32802, LGC-32803 and LGC-32801. The main biliary radioactive components were LGC-32801 (2.2-6.3% and 2.7-3.0% of administered low- and high-dose, respectively) and LGC-32794 (4.7-6.7% and 3.0-4.0% of administered low- and high-dose, respectively).

C. **STUDY DEFICIENCIES:** A minor study deficiency is that the author did not provide "Reference 1" cited in MRID 46378533 to aid in the analysis of metabolism.

57